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Individuals with filaggrin-related eczema and asthma have increased long-term medication and hospital admission costs

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Summary

Background Eczema and asthma are chronic diseases with onset usually before the age of 5 years. More than 50% of individuals with eczema will develop asthma and/or other allergic diseases. Several loss-of-function mutations in filaggrin (FLG) have been identified in patients with eczema. However, the association of *FLG* with healthcare use is unknown.

Objectives To determine whether *FLG* mutations are associated with increased prescribing for eczema and asthma and whether increased prescribing is associated with increased healthcare costs.

Methods A secondary analysis of BREATHE, a cross-sectional study of gene–environment associations with asthma severity, was undertaken. BREATHE data was collected for 1100 participants with asthma, in Tayside and Fife, Scotland during the period 2003–2005. Through collaboration with the Health Informatics Centre in Dundee, BREATHE was linked to accident and emergency, community prescribing and Scottish morbidity records. The data linkage allowed longitudinal exploration of associations between genetic variation and prescribing.

Results An association was found between *FLG* mutations and increased prescribing for mild and moderate eczema, asthma-reliever medicine and asthma exacerbations. A strong association was found between *FLG* mutations and prescribing of emollients [incidence rate ratio (IRR) 2·19, 95% confidence interval (CI) 1·36–3·52], treatment for severe eczema (IRR 2·18, 95% CI 1·22–3·91) and a combination of a long-acting β_2-agonist and corticosteroids (IRR 3·29, 95% CI 1·68–6·43).

Conclusions The presence of *FLG* mutations in this cohort is associated with increased prescribing for eczema and asthma. Randomized controlled trials are required to determine if these individuals could benefit from management strategies to reduce morbidity and treatment costs.

What's already known about this topic?

- Defects in *FLG* are associated with the development of eczema in children.
- Defects in *FLG* are associated with severe and persistent eczema and severe asthma.

What does this study add?

- Patients with *FLG* mutations were dispensed more prescriptions for both eczema and asthma and had more asthma exacerbations over a 9-year period of study.
- This translates into higher long-term costs for these patients.

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- Children and adults with *FLG* mutations may benefit from targeted treatment regimens that could reduce morbidity and treatment costs in this subgroup.

Eczema and asthma are common chronic diseases.[1,2] Eczema affects 15–20% of schoolchildren and 2–10% of adults and asthma affects 16–18% of the U.K. population.[2–4] Almost three-quarters of children with early-onset eczema, a severe and persistent form of eczema, will develop asthma in later life.[5,6]

Eczema and asthma result from a combination of genetic and environmental factors and are treated by a stepwise approach. Eczema is treated initially with emollients followed by the addition of topical corticosteroids (TCS). The strength of prescribed TCS increases with the severity of eczema. Antihistamines may be prescribed to help pruritus. Additional treatment includes topical calcineurin inhibitors and wet wrapping with bandages or eczema garments.[7] Asthma treatment follows the British Thoracic Society (BTS) guidelines, with short-acting β_2-agonists (SABA) as step one. Regular inhaled corticosteroids (ICS) are added in children with frequent SABA use (BTS step two). With increasing disease severity, long-acting β_2-agonists (LABA), leukotrienes receptor antagonists (LTRA), theophyllines and immunosuppressants are added as subsequent steps.[2,8]

In the past decade, several studies[9–17] have shown an association of *FLG* mutations and severe and persistent eczema, however, the strength of the association is unclear. One study did not find an association between the presence of FLG mutations and eczema severity[18] and several studies were cross-sectional. Therefore, to achieve a clearer understanding of the role of *FLG* mutations in eczema and asthma in childhood further exploration of the associations of these mutations with longitudinally measured outcomes was needed, particularly looking at prescribing costs. Although asthma severity, measured as a higher BTS asthma treatment step or risk of asthma exacerbations, has also been associated with *FLG* mutations in individuals with and without eczema,[11,16] the role of *FLG* mutations on prescribing-related outcomes in childhood asthma has not been explored.

The tracking of filaggrin-related eczema and asthma, in comparison with filaggrin-unrelated eczema and asthma, may reveal different long-term patterns of prescribing and other healthcare use for the two genetically distinct forms of the diseases. One measure of assessing healthcare use and medication costs is through analysis of dispensed prescriptions.[19–21] This refers to a prescription both issued by the physician and collected by the patient, from a pharmacist. Existing prescribing databases have tracked dispensed prescriptions in Tayside for several decades, thus providing a unique opportunity to explore differences in prescription use according to *FLG* genotype for both eczema and asthma in BREATHE.[16,22–24] The aim of this study was to determine whether *FLG* mutations are associated with increased prescribing of medication for eczema and asthma and/or an increased number of asthma exacerbations and whether this translates into different healthcare costs.

Patients and methods

BREATHE is a cross-sectional study of gene–environment interactions in 1100 children and adults with physician-diagnosed asthma aged between 2 and 22 years. Study recruitment and initial data collection was undertaken in 2003 to 2005. One of the genes investigated in BREATHE was *FLG*. Collaboration with the Health Informatics Centre in Dundee, Scotland, provided an opportunity to link all participants in BREATHE with the Scottish morbidity records–01 database, the accident and emergency database of Tayside and the community pharmacy database. Through this linkage, it was possible to explore longitudinally the variations in prescribing and other health outcomes. Only patients with a valid community health index number, a unique identifier similar to the National Health Service (NHS) number in England, were included in the cohort. All participants were followed for 9 years, from 2005 to 2013.

Four *FLG* polymorphisms, common in a white population were considered: R501X (rs61816761), 2281del4 (rs41370446), S3247X (rs150597413) and R2447X (rs138726443). Individuals ($n = 23$) with no signal/amplification for any of the four *FLG* polymorphisms were excluded from subsequent analysis. Each polymorphism considered had a genotype call rate of 99% and the minor allele frequency was greater than or equal to 1%. The Hardy–Weinberg equilibrium was tested for each polymorphism. A deviation was seen for R501X and S3247X; however, variants associated with the disease are overrepresented in patients and will show a deviance from Hardy–Weinberg equilibrium. Therefore, these polymorphisms were not excluded from the analysis.[25] For the analysis, the effect of having at least one of the four polymorphisms was compared with the effect of having no polymorphisms. Additional variables were determined from the literature and included: family history of eczema and asthma, cat ownership, age, sex and self-report of eczema. Genotyping for the *FLG* polymorphisms was performed as described in earlier publications.[11,12,16]

The methodology for determining prescription dispensement in relation to clinical outcomes has been well-validated in Dundee.[19–21] Dispensed prescriptions were grouped into eczema or asthma medications by a dermatologist (J.F.) and paediatricians (K.F. and S.M.) according to the *British National Formulary* guidelines and are representative of common practice

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within the U.K. The eczema-related medicines were classified as: emollients, antihistamines and other treatments for mild, moderate and severe eczema (Table S1; see Supporting Information). Asthma-related prescriptions were divided into reliever medicine (SABA and ipratropium bromide) and controller medicines (ICS; LABA; a combination of LABA with ICS; long-acting antimuscarinic (LAMA) controller and LTRA) (Table S2; see Supporting Information). LAMA controller medicine is used only in adults; therefore, the number of LAMA prescriptions in this cohort is small. This group of medicine was not analysed as only five individuals had LAMA controller prescriptions. Asthma exacerbations were defined as asthma-related hospital admissions and/or dispensement of a short course of prednisolone, an oral corticosteroid usually prescribed for asthma attacks.[16]

All statistical analysis was performed using Stata 14.0 (StataCorp, College Station, TX, U.S.A.) and R 3.2.2 (R Foundation, Vienna, Austria). The four polymorphisms were combined into two categories: no *FLG* mutation vs. one or more *FLG* mutations. The outcomes are the number of prescriptions dispensed and asthma exacerbations per patient for each year. The analyses regarding eczema were performed on individuals with eczema and asthma; 530 children and adults, and the analyses concerning asthma were performed on the entire cohort of 978 children and adults. Negative binomial regression was used to model overdispersed (i.e. variance greater than the mean) count outcomes. A negative binomial model with a random effect for the patient was found to be the most adequate to assess the association between *FLG* mutations and prescribing for eczema and asthma, and with asthma exacerbations. Incidence rate ratios (IRRs) were estimated for all variables. Each of the models was adjusted for age, sex, *FLG* status and cat ownership. The P-values were not adjusted for multiple testing as, despite reducing the risk of a type I error, this increases the type II error.[26,27] Instead, we focused on the effect estimation of the association and its magnitude. An IRR between 0·5 and 2 (excluding 1, no association) was defined as a weak-to-moderate association, whereas, an IRR outside these limits was considered a strong association.[28,29]

A cost analysis was performed on the prescribed medication based on Scottish (Information Service Division) prices obtained from 2005 to 2013, expressed in 2014 pounds sterling (see Tables S1 and S2 in the Supporting Information for the range of prices for each pharmaceutical compound. Variations in price for a pharmaceutical compound were because of different strengths and different formulation codes). Costs for hospital admission were only obtained for Fife in 2015 (in the case of hospitalizations, the daily cost of inpatient admission for paediatrics was £477 and the price of a day case was £77. The daily cost of an attendance at the accident and emergency department was £1070). We estimated the prices would not vary significantly over the 9-year period and between Fife and Tayside. All individuals were included in the analysis, regardless of having dispensed a prescription or not, to get an estimate of the cost of eczema for anyone with the condition. To estimate the difference in costs for asthma exacerbation, only individuals admitted to the hospital with an asthma-related event as the main cause were considered. A bias-corrected and accelerated (BCa) bootstrapped t-test was used to obtain confidence intervals (CI) for the means.[30] The BREATHE study and subsequent analyses have approval from the Tayside Medical Research and Ethics Committee.

Results

Of the 1100 children and young adults in the dataset, 23 individuals were excluded as they lacked genotyping information and 99 individuals were excluded because of missing clinical information. The final dataset included 978 children and adults with asthma. Participants were asked whether they, or their child, had eczema, at study collection, and 530 (54·2%) answered positively.

Of the 530 children with eczema and asthma, 43 (8·1%) had not had an eczema-related prescription during the 9-year period. We anticipated that some children reported not to have eczema would develop eczema over the follow-up. Analysis of prescriptions dispensed over the 9-year period revealed two individuals with severe eczema who were probably misclassified and 12 who probably had a mild form of eczema. Table 1 presents the characteristics of the study population.

Table 1 Characteristics of BREATHE study participants

Variable	BREATHE (n = 978)	Patients with eczema (n = 530)	Patients without eczema (n = 448)
Age, at data collection, median (IQR)	10 (7–13)	10 (7–13)	10 (7–13)
Male patients	584 (59·7)	323 (60·9)	261 (58·2)
Individuals with *FLG* mutations	163 (16·7)	119 (22·4)	44 (9·8)
Cat owners	253 (25·9)	124 (23·4)	129 (28·8)
Children and young adults with parental family members with eczema	202 (20·6)	137 (25·8)	65 (14·5)
Children and young adults with parental and nonparental family members with asthma	607 (62·1)	338 (63·8)	269 (60)

Values are n (%) unless otherwise stated. IQR, interquartile range.

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Eczema-related prescriptions

Overall, *FLG* mutations were associated with the number of eczema-related prescriptions during the follow-up (IRR 1·55, 95% CI 1·11–2·16) (Table 2). Age and sex were also related to the number of eczema-related prescriptions; these associations were weak-to-moderate (Table 2). A stronger association was found between the presence of *FLG* mutations and the number of emollients dispensed (IRR 2·19, 95% CI 1·36–3·52), and the presence of *FLG* mutations and the number of prescriptions dispensed for severe eczema (IRR 2·18, 95% CI 1·22–3·91) (Table 2). A weak-to-moderate association was found between the presence of *FLG* mutations and the number of mild and moderate prescriptions dispensed for eczema (Table 2). There was no evidence of an association between the presence of *FLG* mutations and the number of antihistamines dispensed (Table 2).

Table 2 Association between the number of eczema-related prescriptions and *FLG* in individuals with eczema and asthma

Variables	Incidence rate ratio	95% confidence interval	P-value
All eczema-related prescriptions			
Study year	1·00	(0·96–1·05)	0·87
FLG (no vs. yes)	1·55	(1·11–2·16)	0·01
Age (years)	0·96	(0·93–0·99)	0·02
Sex (male vs. female patients)	1·52	(1·14–2·03)	0·004
Cat (no vs. yes)	0·85	(0·61–1·20)	0·36
Antihistamine prescriptions			
Study year	0·97	(0·92–1·03)	0·34
FLG (no vs. yes)	1·23	(0·82–1·85)	0·32
Age (years)	0·96	(0·92–1·00)	0·06
Sex (male vs. female patients)	1·46	(1·03–2·06)	0·03
Cat (no vs. yes)	0·78	(0·52–1·17)	0·22
Emollient prescriptions			
Study year	1·00	(0·93–1·07)	0·95
FLG (no vs. yes)	2·19	(1·36–3·52)	0·001
Age (years)	0·90	(0·86–0·95)	< 0·001
Sex (male vs. female patients)	1·74	(1·15–2·63)	0·009
Cat (no vs. yes)	0·76	(0·47–1·23)	0·27
Prescriptions for mild eczema			
Study year	0·93	(0·87–0·99)	0·03
FLG (no vs. yes)	1·59	(1·03–2·45)	0·04
Age (years)	0·93	(0·88–0·97)	0·001
Sex (male vs. female patients)	1·98	(1·36–2·88)	< 0·001
Cat (no vs. yes)	0·97	(0·63–1·51)	0·91
Prescriptions for moderate eczema			
Study year	0·93	(0·87–1·00)	0·06
FLG (no vs. yes)	1·86	(1·17–2·96)	0·008
Age (years)	0·99	(0·95–1·05)	0·85
Sex (male vs. female patients)	1·87	(1·24–2·81)	0·003
Cat (no vs. yes)	1·06	(0·66–1·71)	0·80
Prescriptions for severe eczema			
Study year	0·98	(0·90–1·07)	0·63
FLG (no vs. yes)	2·18	(1·22–3·91)	0·009
Age (years)	1·01	(0·95–1·07)	0·88
Sex (male vs. female patients)	1·39	(0·84–2·32)	0·20
Cat (no vs. yes)	1·42	(0·80–2·55)	0·23

Asthma-related prescribing

The presence of *FLG* mutations was associated with the number of all asthma-related prescriptions dispensed (IRR 1·30, 95% CI 1·07–1·58) (Table S3; see Supporting Information). A strong association was found between the presence of *FLG* mutations and the number of LABA with ICS dispensed (IRR 3·29, 95% CI 1·68–6·43) (Table S3). A weak-to-moderate association was also found between age and the number of asthma-related prescriptions (Table S3). Similarly, a weak-to-moderate association was found between the number of relievers dispensed and the presence of *FLG* mutations (Table 3). There was no evidence of an association between the presence of *FLG* mutations and the number of ICS, inhaled LABA and oral LTRA dispensed (Table S3).

Asthma exacerbations

Overall, children and adults with *FLG* mutations had significantly more asthma exacerbations than children and adults without *FLG* mutations (IRR 1·76, 95% CI 1·27–2·45)

Table 3 Difference in cost between children and adults with and without *FLG* mutations, between 2005 and 2013[a]

Variables	Difference in means, £	Bias-corrected and accelerated 95% CI, £
All eczema-related prescriptions	94·56	(17·05 to 208·76)
Antihistamine prescriptions	10·84	(−3·79 to 29·57)
Emollient prescriptions	28·92	(0·47 to 69·21)
Prescriptions for mild eczema	6·33	(−4·14 to 20·96)
Prescriptions for moderate eczema	12·94	(0·05 to 39·32)
Prescriptions for severe eczema	35·53	(6·30 to 82·78)
All asthma-related prescriptions	487·67	(168·74 to 836·07)
Reliever prescriptions	79·06	(32·63 to 160·91)
Corticosteroid prescriptions	−11·81	(−36·82 to 21·89)
Long-acting β_2-agonist prescriptions	−17·00	(−39·99 to 40·85)
Long-acting β_2-agonist with corticosteroid prescriptions	295·21	(107·76 to 491·45)
Leukotriene prescriptions	126·55	(13·69 to 246·44)
Asthma exacerbations	485·11	(55·13 to 1502·65)
Total cost for patients with eczema and asthma	1182·23	(257·82 to 3012·16)
Total cost for patients with asthma	1075·63	(335·47 to 2365·59)

[a]Figures prefixed with a minus sign indicate that the costs in children with *FLG* mutations are less than in children without these mutations. CI, confidence interval.

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(Table S4; see Supporting Information). Age and cat ownership were also associated with the number of asthma exacerbations; these associations were weak-to-moderate.

Healthcare system costing

Over the 9-year period, prescription costs for eczema in children and adults with *FLG* mutations were £95 (BCa CI £17–209) more than children and adults without *FLG* mutations. Over 9 years, the mean cost of eczema-related prescriptions for individuals with *FLG* mutations was £244 compared with £150 of eczema-related prescriptions for those without *FLG* mutations. There was no evidence of a difference in costs for antihistamines and for mild eczema according to *FLG* genotype but a significant difference was found between *FLG* status for the cost of emollients and prescribing for moderate and severe eczema (Table 3).

Over the 9-year period, prescription costs for asthma in children and adults with *FLG* mutations were £488 (BCa CI £169–836) more than children and adults without *FLG* mutations. Over 9 years, the mean cost of asthma-related prescriptions for individuals with *FLG* mutations was £1443 compared with £955 for those without *FLG* mutations. There was no evidence of a difference in costs for ICS and LABA according to *FLG* genotype but a significant difference was found between *FLG* status for the cost of prescribing of relievers, a combination of LABA with ICS and LTRA (Table 3). Over the 9-year period, costs for asthma exacerbation in children and adults with *FLG* mutations were £485 (BCa CI £55–1503) more than children and adults without *FLG* mutations. Over 9 years, the mean cost of asthma exacerbations for individuals with *FLG* mutations was £1013 compared with £528 for those without *FLG* mutations (Table 3).

Regarding children and adults with eczema and asthma, there was a £1182 (BCa CI £258–3012) difference in costs between individuals with and without *FLG* mutations (Table 3). The figure is similar considering individuals with asthma, regardless of having eczema. The costs for children and adults with *FLG* mutations and asthma were £1076 (BCa CI £335–2366) more than those for children and adults without *FLG* mutations (Table 3). See Tables S5 and S6 in the Supporting Information for differences in cost for eczema and asthma prescriptions, respectively, between children and adults with and without *FLG* mutations for each year of the study period.

Discussion

This study shows that over a 9-year period, *FLG* mutations played a role in eczema and asthma phenotype, prescribing patterns and healthcare costs for both eczema and asthma.

A strong association between *FLG* mutations and the prescribing of emollients and treatment for severe eczema has been demonstrated. A good epidermal barrier prevents water loss and the penetration of allergens. However, *FLG* mutations lead to an impaired epidermal barrier and studies have shown that individuals with *FLG* mutations have higher transepidermal water loss, and clinically drier and thicker skin than individuals without such mutations.[31,32] This may explain the higher number of emollients dispensed by adults and children with *FLG* mutations in comparison with those without such mutations. The presence of *FLG* mutations has also been associated with a more severe form of eczema,[9–17] which is concordant with our observations that children and adults with *FLG* mutations dispensed more prescriptions related to severe eczema than individuals with eczema but without such mutations.

Our study also found an association between the presence of *FLG* mutations and an increase in the prescriptions of LABA with ICS. A weak-to-moderate association was found between *FLG* and asthma exacerbations. We have previously reported an association between the presence of *FLG* mutations and a carer- or patient-reported, cross-sectional assessment of asthma severity.[23] Through the relative control of skin-barrier function, the presence of *FLG* mutations could represent a unifying mechanism linking eczema and asthma phenotype.

Regarding costs to the NHS, children and adults with *FLG* mutations incurred higher costs due to a higher number of dispensed prescriptions for eczema and asthma, and asthma exacerbations, than children and adults without *FLG* mutations. It is important to note that physicians were unaware of *FLG* status and prescribed medicine based solely on clinical appearance and symptoms. Over a 9-year period, the healthcare system spent £1000 more to treat individuals with asthma with *FLG* mutations than individuals with asthma without *FLG* mutations.

Our cost analysis was a conservative estimate as it was based on medication and hospital admission costs only; other resource use was considered out of the scope of this analysis. Nevertheless, one can estimate the extra cost of treating individuals with *FLG* mutations for the NHS. In 2016, Scotland's population was estimated at 5·3 million, with 10·6 births per 1000 people. In 2015, a study in Aberdeen estimated eczema prevalence at 29% and asthma prevalence at 19%.[33] Assuming that the prevalence of asthma and eczema in Aberdeen can be generalized to Scotland, one can extrapolate that of the 56 180 children born in 2016, around 16 292 may develop eczema, and 10 674 may develop asthma. Assuming that 40% of children with eczema will also develop asthma, around 6517 children born in 2016 could eventually have both diseases. Table 1 shows the proportion of children and adults with asthma and with *FLG* mutations (16·7%), which correspond to 1783 children with asthma and *FLG* mutations. Using that data and considering the prescribing cost for eczema, asthma and hospitalizations one can extrapolate that over a 9-year period the NHS may spend approximately an additional £1 918 000 (estimates vary between £598 000 and £4 218 000) treating children with asthma and *FLG* mutations than children with asthma without *FLG* mutations.

Our cost analysis also generated wide CIs, bringing more uncertainty to our results, and indicating the considerable variability of costs among patients. Our collaboration with the Health Informatics Centre in Dundee allowed us to analyse the data longitudinally, over a 9-year period. This relatively long period of follow-up was more representative of the natural history of eczema and asthma in childhood and young adulthood.

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A potential weakness of our study is that our definition of eczema relies on carer or patient report and may, on occasion, be subjective. Thus, although parents have positively identified their children as having eczema, 43 children did not have any eczema-related prescriptions over the 9-year period. These children could have had very mild eczema, could have outgrown their eczema, been misclassified or moved outside Scotland, which may have underestimated the real cost of individuals with eczema. Another limitation of our study is that it is impossible to be certain that the prescriptions listed in Table S1 (see Supporting Information) were for eczema and related conditions. As we have mentioned in the legends for Tables S1 and S2, these medicines are eczema- and asthma-related, although some medicines, such as antihistamines, might also be used for related allergic conditions. However, we feel this is a reasonable assumption, as conditions other than eczema that are managed with topical steroids are very uncommon in children (for example, the prevalence of psoriasis in children is around 1%).[34] In addition, as part of the research protocol, the children and/or their carers have already stated whether or not the child participant had eczema.

We wished to replicate our results in independent cohorts within the international Pharmacogenomics in Childhood Asthma consortium,[35] which has genotyped data on 14 619 children and young adults with asthma from 11 different countries. However, from a worldwide search, we were unable to find any cohorts of atopic children genotyped for FLG with longitudinal pharmacy data.

The greater morbidity and the greater costs for filaggrin-related eczema and asthma in comparison with filaggrin-unrelated eczema and asthma could represent a unique opportunity in common chronic diseases such as asthma and eczema for developing targeted management strategies that could influence disease burden in the community. A randomized controlled trial (RCT)[36] and a pilot study[37] have found a delay in the onset of eczema in neonates exposed to daily emollients during an 8- and 6-month period, respectively. It may thus be possible to genotype children for *FLG* mutations at, or soon after, birth and intervene with regular, intensive use of emollients. These results indicate that targeted genotyping in early childhood, if successful in developing interventions that even marginally reduce disease burden, could offer many decades of lower prescribing and reduced hospital costs, thus offering a potential solution to spiralling healthcare expenditure in organizations such as the NHS. Thus, while precision medicine could contribute to the development of novel medication, a major benefit in common chronic disease could be the more rational use of currently available therapies, such as daily use of emollients since birth, leading to major cost savings for healthcare systems and improvements in disease control and quality of life.

There was a need to demonstrate the effect of *FLG* mutations on healthcare costs, as healthcare costs are of major importance to the NHS and any effect on the increase of such costs needed to be either demonstrated or refuted with clarity before proceeding with larger studies that test interventions aiming to lower such costs. It is possible to progress with such studies now that the effect of *FLG* mutations on specific healthcare outcomes has been demonstrated. Thus, a future RCT in children with filaggrin-related eczema could test the benefit from more intensive use of emollients on outcomes such as prescribing and other costs for moderate-to-severe eczema measured over some years.

It will be particularly interesting to test the hypothesis that enhanced skin-barrier function, secondary to increased emollient use, reduces hospital costs from asthma exacerbations and community prescribing costs, thus testing novel treatment strategies that are underpinned by the pathological relationships between *FLG* defects, deficient skin-barrier function and asthma that we have described in this article and in earlier publications.[23,38] The challenge lies in translating results such as ours into large-scale RCTs of targeted interventions in common chronic diseases with robust mechanisms for prospectively measuring treatment costs in the community. Community pharmacy databases that longitudinally track prescription encashment and hospital morbidity records that longitudinally track clinical outcomes may be useful in cost-effectively measuring such outcomes. This is particularly relevant in the context of the role of *FLG* mutations in eczema and asthma, as there is existing evidence that altered epidermal permeability, the primary functional defect resulting from these mutations, can be corrected during early life by the use of emollients.[36,37]

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Table S1 List of all eczema-related medicines, included in the analysis, divided by category.

Table S2 List of all asthma-related medicines, divided by category.

Table S3 Association between the number of asthma-related prescriptions and *FLG* in individuals with asthma.

Table S4 Association between the number of asthma exacerbations and *FLG* in individuals with asthma.

Table S5 Difference in cost for eczema prescriptions between children and adults with and without *FLG* mutations during the study period.

Table S6 Difference in cost for asthma prescriptions between children and adults with and without *FLG* mutations during the study period.

Powerpoint S1 Journal Club Slide Set.

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